

TRANSMITTAL LETTER TO THE UNITED STATES
 DESIGNATED/ELECTED OFFICE (DO/EO/US)
 CONCERNING A FILING UNDER 35 U.S.C. 371

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 U.S. Application No.

International Application. No.
 PCT/JP99/03343

International Filing Date
 June 23, 1999

Priority Date Claimed
 June 26, 1998

09/720301

Title of Invention: MEDICINAL COMPOSITIONS FOR TREATING EVACUATORY INSUFFICIENCY

Applicants For DO/EO/US: Kouji YOSHINAGA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. [] is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. [X] has been transmitted by the International Bureau.
 - c. [] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
 - a. [] are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. [] have been transmitted by the International Bureau.
 - c. [] have not been made; however, the time limit for making such amendments has NOT expired.
 - d. [X] have not been made and will not be made.
8. [] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [] A FIRST preliminary amendment.
14. [] A SECOND or SUBSEQUENT preliminary amendment.
15. [] A substitute specification.
16. [X] A change of power of attorney and/or address letter.
16. [X] Other items or information:
 - a. [] Verified Small Entity Statement.
 - b. [X] Copy of Cover Page of WIPO Publication including an English-language Abstract (1 Sheet).

17. [X] The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)):

CALCULATIONS

Search Report has been prepared by the EPO or JPO.....\$860.00

860.00

International preliminary examination fee paid to

USPTO (37 CFR 1.482).....\$690.00

No international preliminary examination fee paid to

USPTO (37 CFR 1.482) but international search fee

paid to USPTO (37 CFR 1.445(a)(2)).....\$760.00

Neither international preliminary examination fee

(37 CFR 1.482) nor international search fee

(37 CFR 1.445(a)(2)) paid to USPTO.....\$1,000.00

International preliminary examination fee paid to USPTO

(37 CFR 1.482) and all claims satisfied provisions

of PCT Article 33(1)-(4).....\$ 100.00

ENTER APPROPRIATE BASIC FEE AMOUNT

= \$860.00

Surcharge of \$130.00 for furnishing the oath or declaration later than

[] 20 [] 30 months from the earliest claimed priority date

(37 CFR 1.492(e)).

\$

Claims	Number Filed	Number Extra	Rate
Total Claims	4 -20=	0	X \$18.00
Independent Claims	3 - 3=	0	X \$80.00
Multiple dependent claim(s) (if applicable)			+\$270.00
TOTAL OF ABOVE CALCULATIONS			= \$860.00

\$

Reduction by 1/2 for filing by small entity, if applicable.

\$

SUBTOTAL

= \$860.00

Processing fee of \$130.00 for furnishing the English translation later than [] 20 [] 30 months from the earliest claimed priority date

(37 CFR 1.492(f)).

\$

TOTAL NATIONAL FEE

= \$860.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet

(37 CFR 3.28, 3.31).

\$40.00 per property

+

\$

TOTAL FEES ENCLOSED

= \$860.00

Amount to be

refunded

\$

charged

\$

a. [X] A check in the amount of **\$860.00** to cover the above fees is enclosed.

b. [] Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

The Commissioner is hereby authorized to charge any other fees due under 37 C.F.R. §1.16 or §1.17 during the pendency of this application to our Deposit Account No. 06-0916.

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Submitted: December 26, 2000

JC01 Rec'd PCT/PTO 26 DEC 2000

PHARMACEUTICAL COMPOSITION FOR THE THERAPY OF
VOIDING DYSFUNCTION

Technical Field

The present invention relates to a pharmaceutical agent and, more particularly, it relates to a therapeutic agent for voiding dysfunction associated with neurogenic bladder.

Background Art

Bladder and urethra which are called lower urinary tracts participate in a voiding function and the function is governed by the three types of nerves - sympathetic nerve, parasympathetic nerve and somatic nerve (pudendal nerve). Sympathetic nerve participates in accumulation of urine while parasympathetic nerve participates in urination and pudendal nerve is always active during accumulation of urine showing an action of closing the external urethra sphincter muscle (cf. *Rinsho to Kenkyu*, 71(5):1180, 1994).

There are various diseases which cause the urinary dysfunction and main ones are classified into (1) neurogenic bladder caused by cerebrospinal disease, cerebrovascular accident, diabetes mellitus, peripheral nervous disturbance, etc., (2) organic lower urinary tract obstruction such as benign prostatic hyperplasia and urethral stricture and (3) contraction insufficiency of bladder caused by stress urinary

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incontinence in adult females, prostatitis, prostatic cancer and anticholinergic agents as well as others which are called LUTS and there are various mechanisms for onset of urinary dysfunction depending upon the diseases for the cause (cf. *Rinsho to Yakubutsu Chiryō*, 14(4):304, 1995).

For example, in urinary dysfunction associated with prostatic hyperplasia, the urinary dysfunction is generated by both urethral stricture (mechanical obstruction) caused by compression of enlarged prostate and over-shrinkage (functional obstruction) of smooth muscle of prostate accompanied by an increase in α_1 receptors in the enlarged prostate (cf. *Rinsho Kagaku*, 33(12):1542, 1997).

On the other hand, neurogenic bladder is a general term for abnormal urination caused by disorder of sympathetic nerve, parasympathetic nerve, etc. controlling the action of bladder and urethra but it does not stand for localizing and systematic diseases (cf. "Hyojun Hinyōki Kagaku", the fifth edition, published in 1998).

Main diseases which cause neurogenic bladder are (1) encephalopathy such as dementia, cerebrovascular disturbance, cerebral wound, encephalitis, brain tumor, multiple sclerosis, Parkinson disease, Shy-Grager syndrome and olivopontocerebellar atrophy; (2) spondylopathy such as spinal cord injury, spinal cord tumor, spondylitis, myelopathy, vascular disease of spinal cord, spinal cord diseases (such

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as cervical spondylosis, disk herniation and cervical ossification of posterior longitudinal ligament), spina bifida and multiple sclerosis and (3) peripheral nerve disturbance such as diabetes mellitus, operations in pelvic cavity (for radical therapy of uterine cancer and rectum cancer), spinal cord diseases (such as disk herniation, spinal cord stenosis, lumbar separation and spondylolisthesis), Guillan-Barre syndrome, pelvic fracture and cauda equina nerve tumor.

In the urinary dysfunction associated with neurogenic bladder, there are a voiding dysfunction and a strage dysfunction and each of those dysfunction may take place either independently or jointly depending upon phase, site, etc. of the dysfunction. In the voiding dysfunction, symptoms such as retardation of initiation of urination, prolongation of time for urination, intermittent urination, minute urinary stream, etc. appear.

At present, the drugs where the effectiveness in clinic has been confirmed as a therapeutic agent for voiding dysfunction associated with neurogenic bladder in Japan, Europe and U. S. A. are cholinergic drugs only and their effect is to improve the urinary disturbance by recovering the shrinking force of bladder of a low active type where detrusor reflex is lost.

Since there is no animal model for reflecting the symptom

in neurogenic bladder, development of the therapeutic drugs therefor is difficult and, even if a few effective cases were clinically confirmed in some substances other than the above-mentioned cholinergic drugs, no drug which can be competent for practical use as the drug has been obtained yet.

Investigation has been carried out for a possibility for the therapy of neurogenic bladder based upon an improvement of urinary efficiency by a decrease in urethral resistance by administration of an α -receptor antagonists such as phenoxybenzamine and prazosin hydrochloride to adrenergic sympathetic nerve which is abundantly distributed in smooth muscle of neck of urinary bladder and urethra of prostate. However, there has been almost no success as a drug which can be competent in clinic.

There has been a demand for developing a therapeutic drug having a new action mechanism which can be competent in practical use as a therapeutic agent for voiding dysfunction associated with neurogenic bladder.

Disclosure of the Invention

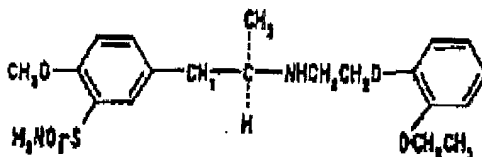
Under such circumstances, the present inventors have found that tamsulosin or a salt thereof is effective for the therapy of voiding dysfunction of the patients with neurogenic bladder.

Thus, the present invention relates to a pharmaceutical

composition for the therapy of voiding dysfunction associated with neurogenic bladder where the composition contains tamsulosin or a pharmaceutically acceptable salt thereof as an effective component.

The present invention further relates to the use of tamsulosin or a pharmaceutically acceptable salt thereof for the manufacture of a therapeutic agent for voiding dysfunction associated with neurogenic bladder. The present invention furthermore relates to a method for the therapy of voiding dysfunction associated with neurogenic bladder where the method includes administration of a therapeutically effective dose of tamsulosin or a pharmaceutically acceptable salt thereof to a patient.

The chemical name for tamsulosin is (R)(-)-5-[2-[[2-(o-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzene-sulfonamide which is represented by the following structural formula. Tamsulosin has been firstly disclosed in the Japanese Laid-Open Patent Publication No.56-110665 together with its pharmaceutically acceptable salts.



Tamsulosin or a salt thereof has been known to have a

blocking action to adrenaline α_{1A} receptor and particularly its hydrochloride (tamsulosin hydrochloride) has been known to have a blocking action to α_1 receptor in urethra and prostate and to reduce the prostatic pressure in the urethral inner pressure curve whereby the urinary dysfunction associated with benign prostatic hyperplasia is improved.

However, there has been no report for confirming the effectiveness to voiding dysfunction associated with neurogenic bladder wherein the onset mechanism is different. Now the present inventors have clinically confirmed for the first time that tamsulosin hydrochloride is effective for the therapy of voiding dysfunction associated with neurogenic bladder.

Incidentally, although there have been several reports for the clinical applications to neurogenic bladder by other α -receptor antagonists such as prazosin hydrochloride, bunazosin hydrochloride, moxisylyte and urapidil, there has been no α -receptor antagonist which can be confirmed to be clinically effective as a therapeutic agent for voiding dysfunction associated with neurogenic bladder in Japan, Europe and U. S. A. For example, with regard to bunazosin hydrochloride, an application for additional use for voiding dysfunction associated with neurogenic bladder was filed with the Ministry of Health and Welfare in Japan but no permission was obtained whereby such an attempt has been given up (cf.

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Asu no Shinyaku, 1998/Pharma Projects).

The present invention will be further illustrated as hereunder.

Tamsulosin and pharmaceutically acceptable salts thereof are easily available either by the methods mentioned in the Japanese Laid-Open Patent Publications No.56-110665 and 62-114952 or by the methods similar thereto.

Tamsulosin is able to form pharmaceutically acceptable acid- and base-addition salts with a large extent of inorganic and organic acids and bases. Such salts constitute a part of the present invention as well. Their examples are salts with inorganic acid such as hydrochloric acid, sulfuric acid and phosphoric acid; salts with organic acid such as fumaric acid, malic acid, citric acid and succinic acid; salts with alkali metal such as sodium and potassium; and salts with alkali earth metal such as calcium and magnesium. The most preferred salt in the present invention is a hydrochloride.

The pharmaceutical agents of the present invention can be prepared as solid preparations for oral use, liquid preparations for oral use or injection preparations by conventional methods using organic or inorganic carriers, vehicles or other additives which are suitable for oral or parenteral administration. Preferred forms are solid preparations for oral use which are able to be taken by the patients themselves and also are convenient for storing and

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carrying and, to be more specific, they are tablets, diluted powder, granules, fine particles, capsules, pills, etc.

In such solid preparations, the active substance is mixed with at least one inert diluent such as lactose, mannitol, glucose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate, etc. The composition may contain additives other than the inert diluent by conventional methods such as a binder (e.g., hydroxypropyl cellulose, hydroxypropyl methyl cellulose, etc.), a lubricant (e.g., magnesium stearate, calcium stearate, polyethylene glycol, starch, talc, etc.), a disintegrating agent (e.g., cellulose calcium glycolate), a stabilizer (e.g., lactose), a solubilizing aid (e.g., glutamic acid, aspartic acid, etc.), a plasticizer (e.g., Tween 80, triacetin, etc.) and a coloring agent (e.g., titanium oxide and iron sesquioxide). If necessary, tablets or pills may be coated with a sugar coat or film soluble in stomach or in intestine such as sucrose, gelatin, agar, pectin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate, etc.

The most preferred form in the present invention is a sustained release preparations of a prolonged release type. Sustained release preparations may be made into tablets, granules, fine particles or capsules by conventional methods. Sustained release preparations are prepared by coating tablets, granules, fine particles or capsules with, for example, fat/oil.

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polyglycerol fatty acid ester, hydroxypropyl cellulose, etc.
by conventional methods.

The sustained release preparation which is disclosed in the Japanese Laid-Open Patent Publication No.62-000009 is particularly preferred. Thus, each unit preparation is prepared in such a manner that a dissolution suppressor is added to a mixture of an active compound and 50% by weight or more of a unit-forming substance in the unit followed by granulating and the resulting particles are filled in a capsule to prepare a capsule preparation or are made into tablets by conventional methods. Crystalline cellulose is preferred as a unit-forming substance. With regard to the dissolution suppressor, water-insoluble high-molecular substance such as acrylate polymer or copolymer or cellulose derivative are used and it is preferred that such a substance is used in a form of an aqueous suspension, an aqueous emulsion or a solution in a water-containing organic solvent. Examples of the commercially available ones are Eudragit L30D-55 (methacrylate copolymer LD), Eudragit E30D (emulsion of copolymer of ethyl acrylate with methyl methacrylate) and Aqua Coat ECD-30 (aqueous suspension of ethyl cellulose) and they are used as dissolution suppressors as they are or after diluting with water if necessary.

The dose of tamsulosin or a pharmaceutically acceptable salt thereof may be appropriately decided for each individual

by taking administration route, symptom of the disease, age of the patient to be administered, sex, etc. into consideration. In the case of oral administration of tamsulosin hydrochloride, the usual dose in terms of the effective component for adult is usually about 0.1 to 0.8 mg/day or, most preferably, 0.2 to 0.4 mg/day and this is orally administered once daily after a meal.

Although the pharmaceutical agent of the present invention is well effective by a single administration, it is also possible that said agent is used together with a cholinergic drug such as distigmine bromide, bethanechol chloride, etc. or with other central nervous system drugs either simultaneously or with time interval. It is further possible that said agent is used together with a therapeutic agent for causal diseases for neurogenic bladder.

Industrial Applicability

In accordance with the present invention, an excellent therapeutic agent for voiding dysfunction associated with neurogenic bladder where said agent is able to be competent for actual use in clinical field can be offered.

Best Mode for Carrying Out the Invention

The present invention will now be further illustrated by way of the following examples and test examples although

the present invention is not limited to those examples, etc.

Example 1.

Tamsulosin hydrochloride (5 g) and 470 g of crystalline cellulose were well mixed and a mixture of 83.3 g of Eudragit L30D-55 (25 g as a solid) with water to make 500 g was added thereto followed by granulating using a high-speed stirring granulating machine. The resulting particles were spherical having a particle size of 0.1-1.5 mm where most of them were in 0.2-1.0 mm.

The resulting particles were mixed with talc and magnesium stearate and the mixture was filled in capsules to prepare the capsule preparation. (Each capsule contained 0.2 mg of tamsulosin hydrochloride.)

Examples 2-6.

The particles which were manufactured by the same manner as in Example 1 according to the formulations of Table 1 were made into the capsule preparations.

Table 1 (unit: grams)

Example Number	Tamsulosin Hydrochloride (g)	Crystalline Cellulose (g)	Eudragit L30D-55 (Solid Content) (g)
2	5	445	166.6 (80)
3	5	395	333.3 (100)
4	5	482.5	41.7 (12.5)
5	2.5	472.5	83.3 (25)
6	1.25	473.75	83.3 (25)

Example 7.

Tamsulosin hydrochloride (5 g), 420 g of crystalline cellulose and 50 g of magnesium stearate were well mixed and

a mixture of 83.3 g of Eudragit L30-D-55 (25 g as a solid) with water to make 500 g was added thereto followed by kneading and granulating using a centrifugal fluidized granulating machine. The resulting particles were spherical having a particle size of 0.1-1.5 mm where most of them were in 0.2-1.0 mm.

The resulting particles were mixed with talc and magnesium stearate and the mixture was filled in capsules to prepare the capsule preparation. (Each capsule contained 0.2 mg of tamsulosin hydrochloride.)

Examples 8-10.

The particles which were manufactured by the same manner as in Example 7 according to the formulations of Table 2 were made into the capsule preparations.

Table 2 (unit: grams)

Example Number	Tamsulosin Hydrochloride	Crystalline Cellulose	Magnesium Stearate	Eudragit L30D-55 (Solid Content)
8	5	480	10	83.3 (25)
9	5	445	25	83.3 (25)
10	2.5	462.5	10	83.3 (25)

Example 11.

Hydrogenated castor oil (80 g) was melted. 10 g of tamsulosin hydrochloride and 30 g of lowly-substituted hydroxypropyl cellulose were dispersed therein and the mixture was made into fine particles by means of a spray congealing. The resulting fine particles (60 g) and 440 g of crystalline cellulose were well mixed, 500 g of water were added thereto

and the mixture was granulated by a centrifugal fluidized granulating machine.

The resulting particles were mixed with talc and magnesium stearate followed by filling in a capsule to prepare a capsule preparation.

Test Example 1. Clinical Test to Patients of Voiding Dysfunction Associated with Neurogenic Bladder.

Clinical test was carried out under the following conditions to the cases of voiding dysfunction associated with neurogenic bladder.

Patients: Sixty patients diagnosed to be voiding dysfunction associated with neurogenic bladder (excluding the cases where the cause was peripheral diseases).

Used drug and method of administration: Capsule preparation containing 0.2 mg of tamsulosin hydrochloride or placebo capsule was used and two capsules were orally administered after breakfast (once daily) for four weeks.

Test period: (1) Wash-out stage: When any therapeutic drug to the disease was given previously, a wash-out period for seven days or longer before starting the observing stage was provided; (2): Observing stage: The observing stage was three days or longer and, when stabilization of the subjective symptoms were confirmed, the therapeutic stage was started; (3): Therapeutic stage: The therapeutic stage was four weeks (28 days).

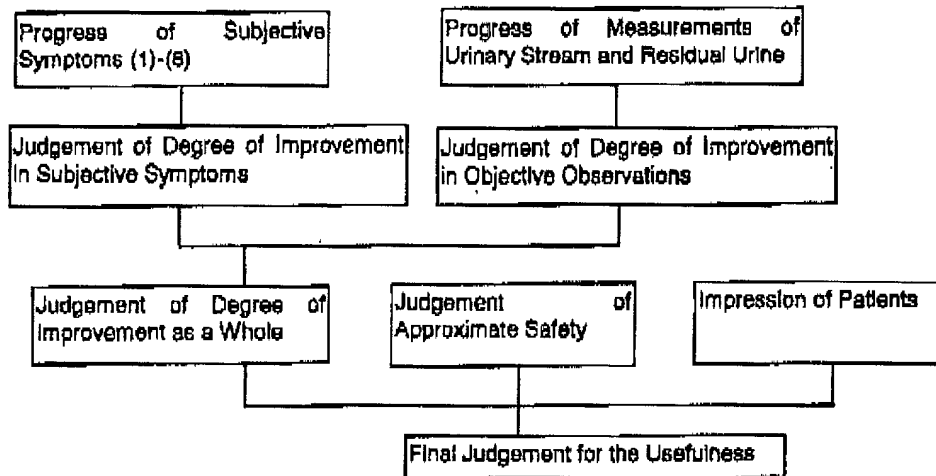
Observing Items and Terms:

Test Items	Wash-Out Stage	Observing Stage	Therapeutic Stage		
	≥ 7 Days	≥ 8 Days			
	-10 Days	-3 Days	0 Day	2 Weeks	4 Weeks (Completion)
Measuring Intracystic Pressure					
Subjective Symptoms*)				●	●
Impression by Patients				●	●
Measuring Urinary Flow + Residual Urine				●	●
Blood Pressure + Heart Rate					●
Clinical Test					●
Side Effect / Accidental Symptom					

*) Subjective Symptoms: (1) Frequency of urination at daytime; (2) Frequency of urination at night; (3) Self-catheterization; (4) Retardation in initiation of urination; (5) elongation of urination time; (6) Strain upon urination; (7) Stoppage of urinary stream; (8) Vigor or dash of urination; (9) Frequency of urinary incontinence.

Method of Evaluation: Evaluation was done according to the following flow chart.

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Result: Table 3 shows the progress of the subjective symptoms (1)-(8) in terms of changing rate (decreasing rate) of the total score and the progress of the urinary flow and residual urine in terms of changing amounts of maximum flow stream rate, average urinary flow rate and residual urine rate.

Table 3

	Tamsulosin Hydrochloride-Administered Group	Placebo-Administered Group
Total Score (Changing Rate)	-31±34.2% (n=23)	-29±31.9% (n=22)
Maximum Urinary Flow (Changing Amt)	2.5±3.01ml/sec (n=16)	-0.6±7.52ml/sec (n=15)
Average Urinary Flow (Changing Amt)	1.2±1.86ml/sec (n=16)	-0.2±4.26ml/sec (n=15)
Residual Urine Amount (Changing Amt)	-18±80.1ml (n=23)	-55±126.8ml (n=15)
Residual Urine Rate (Changing Amt)	-13±20.0% (n=16)	-4±24.1% (n=15)

Degrees of improvement in subjective symptoms and objective observation and degree of improvement as a whole were evaluated as significant improvement, medium improvement,

light improvement, unchanged and worsening depending upon the above-mentioned result.

Approximate safety was evaluated as no problem, little problems, some problems and problems according to the presence/absence and degree of side effect, change of blood pressure and pulse rate, and abnormal change in clinical data.

Impression by the patient was judged to be much improvement, improvement, some improvement, no change, some worsening, worsening and much worsening.

Finally, degree of improvement as a whole, approximate safety and impression by patient were taken into consideration and the final judgement for the Usefulness was judged to be any of the five groups - very useful, useful, somewhat useful and not preferable.

With regard to the approximate safety and impression by patient, there was no significant difference between the groups administered with tamsulosin hydrochloride and with placebo.

The result is shown in Table 4.

Table 4

		Tamsulosin Hydrochloride- Administered Group	Placebo- Administered Group
Degree of Improvement in Subjective Symptoms	\geq Medium Improvement	43.5% (10/23)	31.8% (7/22)
Degree of Improvement in Objective Observation	\geq Medium Improvement	60.0% (12/20)	23.5% (4/17)
Degree of Improvement as a Whole	\geq Medium Improvement	60.0% (12/20)	23.5% (4/17)
Usefulness	\geq Useful	52.2% (12/23)	17.8% (3/17)

Tamsulosin hydrochloride showed significant improvement in the improvement of subjective symptom and objective observation of the patients suffering from voiding dysfunction associated with neurogenic bladder and also in the improvement as a whole. When the impression by the patients was further taken into consideration, it was confirmed that tamsulosin hydrochloride was useful as a therapeutic agent for voiding dysfunction associated with neurogenic bladder.

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Claims

1. A pharmaceutical composition for the therapy of voiding dysfunction associated with neurogenic bladder where said composition contains tamsulosin or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition for the therapy of voiding dysfunction associated with neurogenic bladder according to claim 1 in which said composition contains tamsulosin hydrochloride.

3. The use of tamsulosin or a pharmaceutically acceptable salt thereof for the manufacture of a therapeutic agent for voiding dysfunction associated with neurogenic bladder.

4. A method for the therapy of voiding dysfunction associated with neurogenic bladder where said method includes administration of tamsulosin or a pharmaceutically acceptable salt thereof to a patient.

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Abstract

A therapeutic agent for voiding dysfunction associated with neurogenic bladder where said agent contains tamsulosin or a pharmaceutically acceptable salt thereof.

Declaration and Power of Attorney for Patent Application

特許出願宣言書

Japanese Language Declaration

私は、下欄に氏名を記載した発明者として、以下のとおり宣言する：

私の住所、郵便の宛先及び国籍は、下欄に氏名に続いて記載したとおりであり、

名称の発明に関し、請求の範囲に記載した特許を求める主題の本来の、最初にして唯一の発明者である（一人の氏名のみが下欄に記載されている場合）か、もしくは本来の、最初にして共同の発明者である（複数の氏名が下欄に記載されている場合）と信じ、

排出障害治療用医薬組成物

その明細書を

（該当する方に印を付す）

☐ ここに添付する。

☒ 1999年6月23 日に出願番号

第 PCT/JP99/03343 号として提出し、

日に補正した。

（該当する場合）

私は、前記のいかなる補正書により補正した前記明細書の内容を検討し、理解したことを陳述する。

私は、連邦規則法典第37部第1章第56条(a)項に従い、本願の審査に所要の情報を開示すべき義務を有することを認める。

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

PHARMACEUTICAL COMPOSITION FOR THE

THERAPY OF VOIDING DYSFUNCTION

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on June 23, 1999 as

Application Serial No. PCT/JP99/03343

and was amended on

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

Japanese Language Declaration

私は、合衆国法典第35部第119条にもとづく下記のいかなる外国特許出願または発明者証出願の外国優先権利益を主張し、さらに優先権の主張に係わる出願の出願日前の出願日を有するいかなる外国特許出願または発明者証出願を以下に明記する：

Prior foreign applications
先の外国出願

Pat. Hei-10-179497	JAPAN	26, June, 1998
(Number) (番号)	(Country) (国名)	(Day / Month / Year Filed) (出願の日/月/年)
(Number) (番号)	(Country) (国名)	(Day / Month / Year Filed) (出願の日/月/年)
(Number) (番号)	(Country) (国名)	(Day / Month / Year Filed) (出願の日/月/年)

Priority claimed
優先権の主張

<input checked="" type="checkbox"/> Yes あり	<input type="checkbox"/> No なし
<input type="checkbox"/> Yes あり	<input type="checkbox"/> No なし
<input type="checkbox"/> Yes あり	<input type="checkbox"/> No なし

私は、合衆国法典第35部第120条にもとづく下記の合衆国特許出願の利益を主張し、本願の請求の範囲各項に記載の主題が合衆国法典第35部第112条第1項に規定の態様で先の合衆国出願に開示されていない限度において、先の出願の出願日と本願の国内出願日またはPCT国際出願日の間に公表された連邦規則法典第37部第1章第56条(a)項に記載の所要の情報を開示すべき義務を有することを認める：

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)
(出願番号)

(Filing Date)
(出願日)

(現況) (Status)
(特許済み、係属中、放棄済み) (Patented, pending, abandoned)

(Application Serial No.)
(出願番号)

(Filing Date)
(出願日)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application, or any patent issued thereon.

Japanese Language Declaration

委任状：私は、下記発明者として、以下の弁理士及び代理人、またはそのいずれかをここに選任し、本願の手続きを遂行すること並びにこれに関する一切の行為を米国特許商標庁に対して行うことを委任する。(代理人氏名及び登録番号を明記のこと)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list agent's name(s) and registration number(s))

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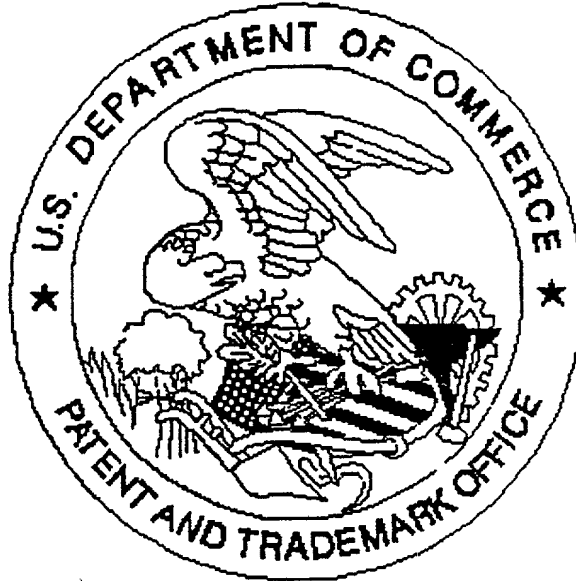
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